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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/170,344	03/30/94	KAST	W D45113TFM

EXAMINER
MINNIFIELD,N

18M1/0614

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ART UNIT	PAPER NUMBER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2-26-96.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 2, 4-18, 25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 2, 4-18, 25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-409-290/40029

Part III DETAILED ACTION

Response to Amendment

15. Applicants' amendment filed February 26, 1996 is acknowledged and has been entered. Claims 1, 19-22, and 24 have been cancelled. Claims 2-8 and 10-18 have been amended. New claim 25 has been added. Claims 2, 4-18, and 25 are now pending in the present application. All prior rejections are withdrawn with the exception of those discussed below.

16. The text of the 35 U.S.C. Code not included in this Office Action can be found in the prior Office Action.

17. The information disclosure statement filed January 4, 1994 fails to comply with 37 CFR § 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicants state (April 17, 1995) that a substitute IDS will be filed, however it has not been received.

The present amendment filed (2-26-96) directed the Examiner to the April 7, 1995 amendment with respect to the content and relevance of the publications referred to in the IDS. The IDS references that have not been considered are EP0375555 and EP0456197. Applicants have not provided an english translation nor a statement of content and relevance of these references in any of the amendments. These references have not been considered as to the merits.

18. The objection to the specification and rejection of claims 2, 4-18 (and now claim 25) under 35 U.S.C. § 112, first paragraph (i.e. lack of an enabling disclosure) is maintained.

This rejection is maintained for essentially the same reasons as the rejection of claims 1-22 and 24 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The disclosure is enabled for nonapeptide sequences from the E6 or E7 genes of HPV16 or HPV18, and MHC Class I molecules as specifically taught in the specification. The specification has not provided sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. Matlashewski et al. discloses that HPV18 proteins (E6 gene) maybe diagnostically useful since the proteins have been identified in specific human cancers, however the methods as claimed in this invention are not known in the art. Accordingly, amendment of the claims to what is supported in the specification or filing of evidence in the form of a Rule 132 declaration providing factual evidence supporting the broad range claims is suggested.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Where the constitution and formula of a compound is stated only as probability and speculation, the disclosure is not sufficient to support claims identifying the compound by

such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the compound. Incomplete teachings may not be completed by reference to subsequently filed applications.

The instant specification invites the skilled artisan to experiment. The factor which must be considered in determining undue experimentation are set forth in Ex parte Forman 230 USPQ 546. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art and the 7) breath of the claims. With regard to factors three and six, it is noted that there are no working examples or support for in vivo efficacy of the active ingredients in a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition, or peptides from any HPV that bind to MHC Class I molecules. Such is not seen as sufficient to support the breath of the claims, wherein the scope of the claims encompasses how to prepare a peptide from any of the listed HPV proteins (or any other HPV protein) wherein the peptide binds to any human MHC Class I molecule. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Applicants have argued that the specification is enabled and have cited Ruppert et al., Kast et al., Feltkamp et al., Vitiello et al., and Ressing et al. as support to demonstrate enablement, however it is noted that the specification must be enabled as of its filing date. Prior art references that were published after Applicants' effective filing date (5-5-92) cannot be used to rebut prima facie case of nonenablement under 35 USC 112. In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

Applicants have argued that it would be unethical to demonstrate HPV treatment in humans, however the Examiner has not suggested such a demonstration. Applicants have not demonstrated treatment of HPV in animal models. With regard to the method of

prophylactic or therapeutic treatment, it appears that the specification is a paper protocol. The specification does not show any therapy or prophylactic treatment, only in vitro studies; no animal studies using the peptides to demonstrate prophylactic or therapy treatment that would correlate to human efficacy have been set forth in the specification.

Applicants have argued that Kast et al. (1991, PNAS 88:2283-2287 and 1991, Immunol. Letters 30(2):229-232) show that one of skill in the art would readily understand from these references how to make and use the claimed invention. Kast et al. (1991, PNAS) disclose the immunization of synthetic peptides of Sendai virus, not HPV. Further, Kast et al. (1991, Immunol. Letters) does disclose the use of peptide vaccination, however the use of HPV peptides is not discussed. HPV is discussed with regard to using "... cultured human CTL for immunotherapy of virus-induced tumors" (p. 229). Furthermore, the reference discloses that there are several unanswered questions regarding peptide vaccination as a novel immunotherapeutic or preventive approach in man (summary; p. 230, col. 2).

In response to Applicant's argument that Matlashewski et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides that bind in the groove on top of an MHC Class I molecule) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that as the methods claims directed to methods of prophylactic or therapy treatment of a human have been cancelled that this objection should be eliminated. However, claims (16-18) directed a pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant are not enabled for the same reasons as methods claims. The claims as presently written indicate or suggest that the 'pharmaceutical composition' would be administered to an animal or human,

however the specification is not enabled for such administration as previously indicated. Further, such short peptides require immunogenic carriers to ensure an immune response.

The claims also recite fragments, homologs, isoforms, derivatives genetic variants or conservative variants of the amino acid sequences and that these fragments, homologs, isoforms, derivatives genetic variants or conservative variants of the amino acid sequences will bind to the grooves on top of the MHC Class I molecule. The specification discloses that variants and derivatives include any amino acid substitution, deletion, or other processes (p. 17). Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (Bowie et al. 1990; p. 1306; p. 1308) and is well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in protein and the result of such modifications is unpredictable based on the instant disclosure.

The specification does not support the broad scope of the claims which encompass all variants of the protein because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity of the intact protein; and the specification provide essentially no guidance as to which

of the essentially infinite possible choices is likely to be successful. Further, Houghten et al. teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al. teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the derivatives that retain immunodominant regions and immunological activity if the regions have been altered.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions encompassing a variant, fragment, derivatives, homologs, isoforms etc as presently claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the protein structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed peptides, for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

19. Claims 12 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

This rejection is maintained. It is noted that Applicants attempted to amend these claims with regard to the Markush language, however the instruction for the amendment of these claims is unclear. The line numbers stated in the amendment filed February 26, 1996 are not the same as those in the amendment filed July 18, 1994.

20. The rejection of claims 2, 4, 7, 8, 11, 13, and 15-18 (and now 25) under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over Schoolnik et al. is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 1, 2, 4, 7, 8, 11, 13, and 15-22 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Schoolnik et al. discloses synthetic peptides from HPV that are useful in the diagnosis and therapy of conditions associated with HPV infection (abstract; p. 9, l. 10-18; claims). Schoolnik et al. teaches the preparation of peptides from HPV16 (E6 and E7) or other HPV proteins useful to raise antibodies for diagnostic, protective (i.e. prophylactic), and therapeutic purposes and vaccines, as well as various mode of administration (p. 3, l. 1-39; p. 5, l. 28-50; p. 4, l. 27 to p. 5, l. 24; p. 7, l. 47 to p. 8, l. 8).

It is noted that the claims recite a peptide comprising an amino acid sequence from a protein of E6 or E7 of HPV 16 or HPV 18.

The teachings of Schoolnik et al. anticipates the claimed invention by disclosing a peptide from a HPV protein wherein the peptide binds to a MHC Class I molecule, and a

method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. The compositions and methods disclosed in Schoolnik et al. are believed to inherently possess properties which anticipates the claimed invention or if they are not the same the composition and methods, the HPV peptides (and compositions) and methods of treatment as disclosed by Schoolnik et al. would none the less render the claims obvious because it possesses the components necessary to prepare a peptide from HPV and methods of treatment as claimed in the instant application. Binding of MHC Class I molecules via T-cell activation is an inherent part of the process of generating an immunogenic response in a mammal. Since the Office does not have the facilities for examining and comparing applicants' method for preparation of a HPV peptide and methods of treatment of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed product and the product of the prior art (i.e., that the peptide, composition, and method of use of the prior art does not possess the same material structural and functional characteristics of the claimed composition and methods of preparation). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

In response to Applicant's argument that Schoolnik et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides have to fit snugly in the groove of HLA Class I molecule; pockets in the groove; specific anchor residues) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

It is noted that the use of prior art published after Applicants' effective filing date can not be used rebut rejections.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants' comments have been addressed previously. Applicants directed the Examiner to the previous response. It is noted at p. 11 of the previous response that

Applicants stated "... one was demonstrated by applicants not to have the binding ability to HLA molecule which is a prerequisite to be a CTL epitope...". Evidence to support Applicants' assertion that the prior art does not anticipated or obviate the claimed invention should be submitted in the form of a declaration.

21. The following new rejection has not been necessitated by the amendment.

22. Claims 2, 4-18 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 and its dependent claims are vague and indefinite in the recitation of "comprising" as the use of the open-ended term "comprises" which fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Claim 25 is directed to a peptide comprising an amino acid sequence derived from a HPV protein wherein the sequence comprises a nonapeptide from E6 or E7 of HPV 16 or HPV 18. Claim 9 is indefinite and lacks proper antecedent basis in that the claim depends from claim 1 which has been cancelled.

23. No claims are allowed.

24. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT

MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield
May 31, 1996

James C. Housel
JAMES C. HOUSEL 6/10/96
SUPERVISORY PATENT EXAMINER
GROUP 180